DECARBOXYLATION AND RECONSTITUTION OF LINOLEIC ACID[1]

Sir:

In search of an approach to the preparation of isotope-labelled linoleic acid more promising than those suggested by recently reported total syntheses of this physiologically and commercially important unsaturated fatty acid,[2,3,4] we have succeeded in showing that the carboxyl group of linoleic acid isolated from natural sources can be removed and replaced, the sensitive and synthetically-imposing unsaturated hydrocarbon moiety being protected during this process by bromination. Starting with the readily purified 115°-9,10,12,13-tetrabromostearic acid (I) (in which form linoleic acid is most commonly isolated from certain saponified seed oils), the process involves the following steps

$$C_5H_{11}(CHBr)_2CH_2(CHBr)_2(CH_2)_7COOH \qquad \text{I}$$
$$\downarrow$$
$$C_5H_{11}(CHBr)_2CH_2(CHBr)_2(CH_2)_7COOAg \qquad \text{II}$$
$$\downarrow$$
$$C_5H_{11}(CHBr)_2CH_2(CHBr)_2(CH_2)_7Br \qquad \text{III}$$
$$\downarrow$$
$$C_5H_{11}CH{=}CHCH_2CH{=}CH(CH_2)_7Br \qquad \text{IV}$$
$$\downarrow$$
$$C_5H_{11}CH{=}CHCH_2CH{=}CH(CH_2)_7MgBr$$
$$\downarrow$$
$$\text{linoleic acid}$$

Treatment of an absolute methanol solution of the ammonium salt of I with another of silver nitrate in the same solvent gives the corresponding silver salt (II). Addition of dry II to a solution of bromine in carbon tetrachloride results in the loss of carbon dioxide and the formation of the 1,8,9,11,12-pentabromoheptadecane III, m.p. 62–64° (*Anal.* Calcd. for $C_{17}H_{31}Br_5$: C, 32.15; H, 4.92; Br, 62.93. Found: C, 32.22; H, 4.89; Br, 62.90). The action of zinc on III results in the regeneration of the *cis,cis*-1,4-diene grouping originally present in the linoleic acid, while the isolated terminal bromine atom is unaffected; the product, 8,11-heptadecadienyl bromide (IV), is a colorless oil, b.p. 131° at 0.15 mm., $n^{25}\text{D}$ 1.4810, d^{26} 1.02145, $M\text{D}$ 87.86 (theory 87.56) (*Anal.* Calcd. for $C_{17}H_{31}Br$: C, 64.75; H, 9.91; Br, 25.34. Found: C, 64.87; H, 9.91; Br, 25.17). The Grignard reagent prepared from IV, on treatment with carbon dioxide, regenerates linoleic acid, identified by virtue of the fact that its infrared absorption spectrum was essentially identical with that of an authentic sample and by the melting point and mixed melting point of the tetrabromostearic acid (I) prepared from it.

Since linoleic acid is reconstituted (by replacement of the carboxyl group as carbon dioxide) in the high-yield last step of the series, this procedure seems ideally suited to the preparation of the carboxyl-labelled substance. Moreover, there seems to be no reason why the method should not be applicable with equal success to other unsaturated fatty acids whose carboxyl labelling would be desirable.

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THE SYNTHESIS OF MORPHINE

Sir:

Racemic β-Δ^6-dihydrodesoxycodeine methyl ether[1] yields with L(+)-dibenzoyltartaric acid only the salt of the *d* base (monohydrate), m.p. 162.5–163°, found C, 65.60; H, 6.07; $[\alpha]^{27}\text{D}$ +44.5° (*c* 1.53, chf.) whose mixed m.p. with natural *d*-β-Δ^6-dihydrodesoxycodeine methyl ether L(+)-dibenzoyltartrate monohydrate of m.p. 163–163.5°, $[\alpha]^{27}\text{D}$ +48° (*c* 1.80 chf.) was not depressed. The infrared spectra of these salts are indistinguishable. Similarly with D(−)-dibenzoyltartaric acid, only the salt of the *l* base, m.p. 161.5–162°, found C, 66.09; H, 6.45, $[\alpha]^{27}\text{D}$ −44° (*c* 1.94 chf.), is obtained. Equal amounts of synthetic *l* salt and natural *d* salt yield inactive β-Δ^6-dihydrodesoxycodeine methyl ether dibenzoylracemate (anhydrous), m.p. 182°, found C, 67.37; H, 6.05, identical in m.p. and mixed m.p. with the product of the synthetic racemic base and dibenzoylracemic acid.

The *d* salt with ammonia yields the *d* base, found C, 76.40; H, 8.51; $[\alpha]^{27}\text{D}$ +80° (*c* 1.24, alc.) m.ps. 43.5–44° and 57.5–58°, dimorphous, whose mixed m.ps. with natural β-Δ^6-dihydrodesoxycodeine methyl ether, found C, 76.49; H, 8.61; $[\alpha]^{27}\text{D}$ +80 (*c* 1.55, alc.) which also exhibits these m.ps., were undepressed. The infrared spectra of these bases are indistinguishable. Confirmation of this identity was obtained through the methiodide, synthetic *d*, m.p. 186.5–188°, natural, 188–189°, mixture undepressed, found C, 54.33; H, 6.51; and the picrate, m.p. synthetic *d*, 227.5–228.5°, natural 230–231°, mixture undepressed, found C, 56.88; H, 5.67.

d-β-Δ^6-Dihydrodesoxycodeine methyl ether on hydration with dilute sulfuric acid yields β-dihydrothebainol methyl ether, m.p. 152–153°, methiodide, m.p. 243–244°, mixed m.ps. with authentic samples[1] not depressed. The infrared spectrum of the base is indistinguishable from that of an authentic sample. On vigorous treatment of this substance with potassium hydroxide in diethylene glycol, demethylation takes place, and from the resulting mixture β-dihydrothebainol, m.p. 165.5–166.5°, methiodide m.p. 266–268°, mixed m.p.s with authentic samples[1] undepressed, can be isolated. Oxidation of this substance by the potassium *t*-butoxide–benzophenone system[2] gives β-dihydrothebainone,[3] perchlorate, m.p. 265–268°, oxime, m.p. 223–226°, mixed m.ps. undepressed.

β-Dihydrothebainone on bromination with two moles of bromine followed by treatment with 2,4-

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